REMARKS

Applicant respectfully requests reconsideration. Claims 26-48 were previously pending in this application. Claim 26 is amended herein. As a result, claims 26-48 are still pending for examination with claims 26 and 38 being independent claims. No new matter has been added.

Objection to Specification

The Examiner continues to maintain that the specification does not provide antecedent basis for the phrase "wherein the phosphorothioate oligonucleotide is not antisense."

Without conceding the correctness of the rejection and in the interest of expediting prosecution, Applicant has amended claim 26 to recite that the phosphorothioate oligonucleotide analog stimulates the cell-mediated response through a non-antisense mechanism. Support for this amendment can be found on page 8, lines 10-15 of the application as filed. As discussed in the response to the previous Office Action, Applicant had clearly recognized in the specification that the immunostimulatory ability of the claimed oligonucleotides is not related to any antisense effect which these oligonucleotides may or may not possess.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. 112

Claims 26-48 have been rejected under 35 U.S.C. 112, first paragraph, as lacking written description. The Examiner alleges that "the claims encompass thousands of immunostimulatory oligonucleotides that differ in length, sequence, and structure and which generate an immune response" and that "Applicant's reliance on the phosphorothioate backbone as a common structure and the induction of an immune response as a common function of the molecules is not sufficient" (page 5 of the Office Action). Applicant respectfully traverses the rejection.

The objectives of the written description requirement are to clearly convey the information that an Applicant has invented the subject matter which is claimed and to put the public in possession of what the Applicant claims as the invention. Possession of the invention may be shown in a variety of ways including description of an actual reduction to practice, or by describing

distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (MPEP 2163). The application is based, at least in part, on the surprising discovery that oligonucleotide analogs having at least one phosphorothioate bond can induce stimulation of a local immune response. Applicant has disclosed in the specification several phosphorothioate oligonucleotide analogs and their use in promoting cell mediated and local immune responses apart from their ability to produce antisense effect. Specifically, administration of phosphorothioate oligonucleotide analogs were shown to induce a local immune response and resulted in the release of cytokines.

The Examiner asserts that to provide adequate written description and evidence of possession, the specification must provide sufficient distinguishing identifying characteristics of the genus (Page 6 of the Office Action). As discussed above, the application is based, at least in part, on the surprising discovery that oligonucleotide analogs having at least one phosphorothioate bond can induce stimulation of a local immune response. The sequences of phosphorothioate oligonucleotide analogs have been provided in the application. Applicant has disclosed several working examples that demonstrate the ability of such oligonucleotides to induce cell-mediated and local immune responses, irrespective of their antisense effects. The specification describes both structure (an oligonucleotide with at least one phosphorothioate bond) and structure/function correlation (an oligonucleotide with at least one phosphorothioate bond induces an immune response). Thus, the specification as filed adequately establishes the structure/function correlation that would allow one of ordinary skill in the art to envision the phosphorothioate oligonucleotide analogs encompassed by the present claims. Moreover, according to the MPEP, "[w]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. >See also *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005)." At the time of filing of the instant application, oligonucleotides containing phosphorothioate modifications were well known in the art.

The Examiner has alleged that only one phosphorothioate oligonucleotide analog was actually administered and shown to elicit a local immune response (page 7 of the Office Action). Applicant respectfully disagrees. In addition to SEQ ID NO: 1, repeated intradermal administration of ISIS 1082 (SEQ ID NO: 2) to healthy rats with no HSV infections was shown to elicit a local immune response and resulted in the release of cytokines. Thus, even though the rats were not infected with HSV, the HSV antisense ODN (1082) had an immune stimulatory effect (page 15, lines 36-37 of the application as filed). In addition, incubation of ISIS 1082 with an uninfected *in vitro* human skin model derived from neonatal keratinocytes and fibroblasts resulted in a concentration dependent increase of cytokine release (page 15, lines 36-37 and page 16, lines 1-17). Given the absence of any viral infections in the rats and the skin model used in these studies, these examples demonstrate the ability of the oligonucleotide ISIS 1082 (SEQ ID NO: 2) to induce an immunostimulatory response that is unrelated to any antisense effect.

The Examiner asserts that "[s]ome phosphorothioate oligonucleotides do not elicit non-specific effects or immune responses. However, phosphorothioate oligonucleotides elicit sequence specific response" and cites McIntyre et al. (Antisense Research and development 3: 309-322, 1993) in support of this (page 6 of the Office Action). Applicant respectfully disagrees with this broad interpretation of the teachings of McIntyre. As discussed in the previous response filed on July 31, 2006, McIntyre et al. teaches only one oligonucleotide, the p65 sense oligonucleotide, for which the data were interpreted as indicating a sequence-specific immune effect. While McIntyre et al. states that "reports have begun to emerge regarding the usefulness of antisense phosphorothioate oligonucleotides in vivo in diverse models", McIntyre goes on to say that "relatively little is known about the in vivo side effects of these oligonucleotides on different tissues." (McIntyre, page 317-318) . The McIntyre reference cites two other papers (Branda and Mojcik) as saying that their sense oligos have similar sequence-specific effects. However, McIntyre notes that these have no sequence homology with the p65-sense oligo. McIntyre goes on to state that "it is possible that the p65-sense oligonucleotides bind to some unidentified mRNA that includes a natural antisense RNA to p65, thus acting as a synthetic antisense sequence." (page 318).

Wu et al. (Anesthesiology 94: 1119-1132, 2001) has been cited to support the teaching "phosphorothioates molecules may interact non-specifically with cellular targets, resulting in

extensive cellular cytotoxicity". However, Wu et al. support the use of phosphorothioate oligonucleotides for the purpose of sequence-independent immune stimulation, stating that "sequence-independent effects, including immune stimulation...may be caused by the polyanionic character of the phosphorothioate oligonucleotides" (Wu et al., page 1129, right column, first paragraph, second sentence.) Therefore, the teachings of Wu et al. do not support the broad conclusion that the "response due to the administration of a phosphorothioate oligonucleotide analog is sequence dependent."

Applicant respectfully submits that "[s]atisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed" (MPEP 2163). Oligonucleotides containing phosphorothioate modifications were well known in the art at the time of filing of the instant application. The specification provides sufficient data which clearly establishes that the claimed oligonucleotides can produce a cell-mediated immune response that is not related to any antisense effect which these oligonucleotides may or may not possess. Thus, Applicant has demonstrated possession of a class of compounds (oligonucleotides containing phosphorothioate modifications) which can be used according to the methods of the invention. Accordingly, the written description for the claimed methods is met and it is respectfully requested that the rejection be withdrawn.

Claims 26-48 have been rejected under 35 U.S.C. 112, first paragraph, as lacking enablement. The Examiner continues to maintain that "data provided is not commensurate in scope with the claims which are drawn to administering a broad genus of analogs comprising thousands of possible structures." (page 10 of the Office Action). Applicant respectfully disagrees and requests reconsideration of the rejection.

The objective of the enablement requirement is to inform those skilled in the relevant art how to both make and use the claimed invention (MPEP 2164). As discussed above, the application is based, at least in part, on the surprising discovery that oligonucleotide analogs having at least one phosphorothioate bond can induce stimulation of a local immune response. The specification provides sufficient data which clearly establishes that the claimed oligonucleotides can produce a

cell-mediated immune response that is not related to any antisense effect which these oligonucleotides may or may not possess. Moreover, oligonucleotides containing phosphorothioate modifications were well known in the art at the time of filing of the instant application.

The Examiner alleges that "applicant has provided evidence in the specification limited to administration of only one species of phosphorothioate oligonucleotide, ISIS 2105, which is not sufficient to provide enablement for the entire genus of phosphorothioate analogs" (pages 9-10 of the Office Action). According to MPEP 2164.02, "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)." Given that the phosphorothioate oligonucleotide analogs were well known in the art and the data in the specification clearly establishes the ability of the claimed oligonucleotides to induce a cell-mediated immune response, a person of ordinary skill in the art would be able to practice the invention with any undue experimentation. Moreover, contrary to the Examiner's assertion, in addition to SEQ ID NO: 1, repeated intradermal administration of ISIS 1082 (SEQ ID NO: 2) to healthy rats with no HSV infections was shown to elicit a local immune response and resulted in the release of cytokines. Thus, even though the rats were not infected with HSV, the HSV antisense ODN (1082) had an immune stimulatory effect (page 15, lines 36-37 of the application as filed). Incubation of ISIS 1082 with an uninfected *in vitro* human skin model derived from neonatal keratinocytes and fibroblasts resulted in a concentration dependent increase of cytokine release (page 15, lines 36-37 and page 16, lines 1-17). Given the absence of any viral infections in the rats and the skin model used in these studies, these examples demonstrate the ability of the oligonucleotide ISIS 1082 (SEQ ID NO: 2) to induce an immunostimulatory response that is unrelated to any antisense effect. Thus, the evidence provided in the specification is not limited to a single species.

The Examiner cites Ratajczak et al. (PNAS 1992 89:11823-11827) for teaching that "the oligomers had no effect on animal survival or extent of disease (table 1), McCluskie et al. (Vaccine 19:2657-2660, 2001) for the teaching that "a polythymidine nucleic acid twenty nucleotides in length (ODN 1983), which did not have an immunostimulatory effect in immunized mice" and Jones et al. (Vaccine 17:3065-3071, 1999) for teaching "a T-rich immunostimulatory nucleic acid

lacing CpG dinucleotides as a negative control for testing ODNs in vivo". The data provided in all these cited references correspond to a single dose of nucleic acid. Presumably, it is a dose at which the tested CpG nucleic acids were active. However, as argued herein, that dose may not be optimal for a non-CpG nucleic acid such as the phosphorothioate nucleotide analogs of the instant invention. Ratajczak et al., McCluskie et al. and Jones et al. therefore stand for the proposition that higher doses of non-CpG nucleic acids may be necessary for immune stimulation (as compared to CpG nucleic acids). They do not support the proposition that phosphorothioate nucleotide analogs are not immunostimulatory.

The structure of oligonucleotides was known in the art at the time of the invention, as was the structure of a phosphorothioate linkage within a phosphodiester backbone. Moreover, it was routine in the art to make such phosphorothioate linkage containing oligonucleotides. At the time of filing, methods of making and using nucleotide modifications such as altered sugar moieties, inter-sugar linkages and base units were known in the art. The specification further teaches how to test phosphorothioate oligonucleotide analogs for immunostimulatory activity. The specification teaches how such an immunopotentiator can be identified and provides various assays that could be used for this purpose. The specification gives examples of the use of phosphorothioate oligonucleotide analogs to induce an immune response in mice, rats, and humans.

Accordingly, the claimed invention is enabled in its scope with respect to the recited methods of treatment, in view of the teachings of the specification and the knowledge in the art at the time of filing, and withdrawal of this rejection is respectfully requested.

Double Patenting

Claims 26, 28, 29 and 30 have been rejected as being unpatentable over claims 1-8 of U.S. Patent 6,727,230 (Hutcherson, et al.) in view of U.S. Patent 5,356,882 (Walker et al.).

Applicants state for the record that they may consider filing a Terminal Disclaimer if some of the claims are found to be allowable. It is respectfully requested that the rejection be delayed until claims are found to be allowable.

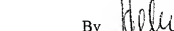
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1037.70049US00.

Dated: September 17, 2009

Respectfully submitted,

By 

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